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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/955,174	09/19/2001	William G. Kerr	PH114205.2402/KMZ15101.02	9411

7590 02/18/2004

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 02/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/955,174	KERR, WILLIAM G.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover she t with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *6,14 and 17-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-13,15 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 September 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5-16-02,2-7-03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 11-6-03.

Claims 1-37 are pending in the instant application.

Election/Restrictions

Claims 6, 14 and 17-37 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the response dated 11-6-03.

Applicant's election without traverse of Group I, claims 1-5, 7-13, 15 and 16, in Paper No. 11-6-03 is acknowledged.

The elected claims have been examined as they read on a genetic construct comprising interfering RNA as set forth below.

Claim Objections

Claims 1-5, 7-13, 15 and 16 are objected to because they recite non-elected inventions. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 5 and 13, lines 4-5, the metes and bounds of "or a combination thereof" cannot be determined (e.g. Does this mean that the combination of an antisense, ribozyme and RNAi, or multiple RNAi components, are all constructed within the same nucleic acid compound? And, if so, do they target the same, overlapping or different regions of the target SHIP mRNA?). Appropriate clarification is requested.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 7-13, 15 and 16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is drawn to compositions and methods for suppressing or preventing a transplant rejection in a patient, or preventing or treating graft versus host disease (GVHD) in a patient comprising the administration of an interfering RNA specific for SHIP mRNA, whereby SHIP expression is inhibited. The specification and claims do not indicate the distinguishing attributes identifying members of the genus comprising

SHIP mRNA (e.g. mRNA of a particular SEQ ID No., or from a particular organism, or a particular isoform such as SHIP-I or SHIP-II, see for example USPN 6,025,198). Concise structural features that could distinguish structures within the genus from others are missing from the disclosure and the claims. The specification fails to teach or adequately describe a representative number of species in the genus such that the common attributes or characteristics concisely identifying members of the proposed genus comprising SHIP mRNA are exemplified. And because this genus is highly variant, the description provided is insufficient. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus claimed. Thus, applicant was not in possession of the claimed genus.

Claims 1-5, 7-13, 15 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for suppressing the rejection of a fully allogeneic bone marrow graft from BALB/C mice in SHIP-/- mice or abrogating GVHD disease in SHIP-/- mice that were transplanted with whole bone marrow from BALB/C mice, thereby enhancing SHIP-/- mice survival, does not reasonably provide enablement for preventing a transplant rejection in any patient, or preventing or treating graft versus host disease (GVHD) in any patient comprising the administration of an interfering RNA specific for SHIP mRNA. The specification does not enable any person skilled in the art to which it pertains, or with which it is most

nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to compositions and methods for suppressing or preventing a transplant rejection in a patient, or preventing or treating graft versus host disease (GVHD) in a patient comprising the administration of an interfering RNA specific for SHIP mRNA, whereby SHIP expression is inhibited in that organism and treatment effects provided.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of oligonucleotides, including interfering RNA, treatment in organisms. Branch and Crooke teach that the in vivo (whole organism) application of nucleic acids is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of *in vivo* inhibition of target genes. (See entire text for Branch and especially pages 34-36 for Crooke). The high level of unpredictability regarding the prediction of antisense or targeting oligonucleotide efficacy, for instance, in treating disease states was illustrated in the clinical trial results obtained by ISIS pharmaceuticals for the treatment of Crohn's disease using antisense targeting ICAM-1, whereby the placebo treatment was found more successful than antisense treatment (BioWorld Today: See entire article,

especially paragraphs 3 and 5-7 on page 1). Additionally, Palu et al teach that the success of gene delivery using virally derived vectors is dependent on the empirical determination of successful gene transduction for a given vector and a given target cell (See entire article, especially page 4, section 2).

Tamm et al, in a review article discussing the therapeutic potential of inhibitory nucleic acids in treating various forms of neoplasia, conclude that "Proof of clinical efficacy, of any of the antisense oligonucleotides in the field of oncology, is still missing." (see especially pages 490-493 for a summary of various clinical trials in process using targeting oligonucleotides). Additionally, Agrawal et al point to various factors contributing to the unpredictability of inhibiting nucleic acid therapy, including non-antisense effects attributed to secondary structure and charge, as well as biological effects exerted by sequence motifs existing within the inhibitory nucleic acid sequences, all providing for unpredictable in vivo side effects and limited efficacy (e.g. see pages 72-76). Agrawal et al speak to the unpredictable nature of the antisense field thus: "It is therefore appropriate to study each antisense oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide." (see page 80).

Cellular uptake of oligonucleotides by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy. Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of oligonucleotides in vitro and in vivo (see Agrawal et al especially at pages 79-80; see Chirila et al in its entirety, especially pages

326-327 for a general review of the "important and inordinately difficult challenge" of the delivery of therapeutic antisense or inhibitory oligonucleotides to target cells).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of inhibiting the expression of any forms of SHIP in vitro or in vivo, comprising the administration of an interfering RNA specific for SHIP mRNA, whereby SHIP expression is inhibited. Applicants have not provided guidance toward a method of treating or preventing a transplant rejection in a patient, or preventing or treating graft versus host disease (GVHD) in a patient comprising the administration of an interfering RNA specific for SHIP mRNA. The specification teaches the suppression of the rejection of a fully allogeneic bone marrow graft from BALB/C mice in SHIP-/- mice, as well as the abrogation of GVHD disease in SHIP-/- mice that were transplanted with whole bone marrow from BALB/C mice, whereby SHIP-/- mice survival was enhanced. One skilled in the art would not accept on its face the examples given in the specification of the enhanced survival and reduction of transplant rejection in a mouse model using SHIP-/- mice as being correlative or representative of the successful inhibition of expression of SHIP in vivo using interfering RNA specific for SHIP mRNA, and further whereby treatment or prophylactic effects are provided for transplant rejection or graft versus host disease (GVHD) in a patient in view of the lack of guidance in the specification and known unpredictability associated with the ability to predict the efficacy of interfering RNA in inhibiting the expression of SHIP in any organism and in treating, suppression or preventing transplant rejection or graft versus

host disease (GVHD) in a patient following administration by any route of the claimed oligoncucleotides. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with in vivo delivery and treatment effects provided by the claimed oligonucleotides administered, and specifically regarding the instant compositions and methods claimed.

The breadth of the claims and the quantity of experimentation required. The breadth of the claims is very broad. The claims are drawn to compositions and methods for suppressing or preventing a transplant rejection in a patient, or preventing or treating graft versus host disease (GVHD) in a patient comprising the administration of an interfering RNA specific for any SHIP mRNA, whereby SHIP expression is inhibited in that organism. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues harboring the target gene or genes SHIP, whereby SHIP expression is inhibited in vitro and in vivo, and further whereby treatment and/or prophylactic effects are provided for transplant rejection or graft versus host disease (GVHD) in a patient. Since the specification fails to provide any particular guidance for the successful targeting and inhibition of expression of any forms of SHIP in vitro or in vivo using the oligonucleotides claimed, or for the successful treatment, suppression or prevention of any transplant rejection or graft versus host disease (GVHD) in an organism, and since determination of these factors is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER

JZ
2-4-04